REMARKS

This amendment is being filed together with a Request for Continued Examination ("RCE"). Upon entry of the above amendment, claims 1 and 16-18 will be pending. Claim 16 has been amended to clarify its scope. Support for the amendment can be found in the specification, for example, at ¶[0039] and ¶[0061]. No new matter has been added.

The Office Action Summary indicates that claims 1 and 16-18 have been rejected. However, the Office Action itself indicates only that claims 16-18 are rejected for alleged lack of enablement and non-statutory obviousness-type double patenting and does not provide information regarding the grounds for the rejection of claim 1. As the Applicant understands the interview summary, claim 1 was found to be allowable. If this understanding is incorrect, clarification regarding the status of claim 1 is requested. This response addresses the rejections to claims 16-18.

Applicant respectfully requests entry of the above amendment and allowance of the claims in view of the remarks in this Response.

Specification

The title has been amended in accord with the Examiner's suggestion. The amended title reads: "Transgenic Mice Expressing Baculovirus Soluble gp64 and Methods of Using Such Mice to Make Antibodies."

Interview Summary

Applicant respectfully disagrees with the Examiner that Applicant has found the Examiner's proposed amendment to be acceptable. Applicant notes that its representative also spoke with the Examiner on May 14, May 15, twice on May 19, once on May 27 and received substantial voicemails from the Examiner on May 22 and June 3. The Examiner's proposed amendment and the terminal disclaimer were discussed. The Examiner also sent his proposed claim amendments in an e-mail on May 15. 2009.

35 U.S.C. §112, first paragraph

The Examiner has rejected claims 16-18 for alleged lack of enablement. As the Applicant understands it, the Examiner bases his rejection on two grounds:

1) that one of skill in the art would have to undertake undue experimentation in order to use an immunogen comprising "i) a baculoviral particle or portion thereof, and ii) a target antigen as broadly claimed." (Office Action at page 2);

2) his concern regarding the dose of baculoviral particles and the structure of the antigen used to immunize the mice in Example 4. He also cites Saitoh (*J. Immunol. Methods* 332: 104-117 (2007) as "post-filing evidence for obtaining antibodies against pepT1" (Office Action at page 4).

Applicant respectfully traverses these rejections. An invention, as defined by the claims, is enabled where one of ordinary skill in the art can make and use it without resorting to undue experimentation. See, *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed.Cir.1988). All of the evidence must be considered, and any conclusion of nonenablement must be based on the evidence as a whole. MPEP § 2164.01(a).

Contrary to the Examiner's assertion, one of skill in the art would be able to practice the claimed methods of producing an antibody without undue experimentation. The Examiner appears to require that any method of making antibodies in the sgp64 transgenic mice of the claims be necessarily limited to a membrane protein that is present both on an intact budding baculovirus particle and that is displayed on the surface of the baculovirus particle that is administered to the sgp64 transgenic animals. The Examiner states that:

> The specification fails to teach how to introduce the target antigen in context of a portion of a baculovirus. The specification fails to teach how to immunize without the target antigen being expressed by the baculovirus particles. The specification fails to teach how to introduce the target antigen expressed inside the baculoviral particle and not with the envelope proteins on the surface of the particle. (Office Action at page 4, emphasis original.)

Applicants remind the Examiner that the general problem the inventors set out to solve was to develop a method of efficiently producing antibodies against virally-expressed target antigens that are typically contaminated with highly immunogenic "background" antigens. The inventors sought to reduce or eliminate the production of antibodies to one such background

antigen, the baculoviral protein, gp64. To that end, the inventors set out to develop, and did develop, mice that were transgenic for the soluble form ("sgp64") of gp64 and thus likely to be immunotolerant for that particular contaminating background antigen. To assist the Examiner, Applicants have provided Exhibit A, a graphic depicting the method of claim 16; please note that the representation is meant to be illustrative and not quantitative. As the Applicants have disclosed, the sgp64 transgenic mice showed immunologic tolerance to gp64 (See Example 4). As the specification indicates at paragraph [0099]: "In the case of non-transgenic mice (non-Tgm), staining with anti-mouse IgG resulted in strong staining for all three mice" (See lanes #5, #6 and #8 of Figure 3). In contrast, "[T]here was hardly any gp64 staining for the sgp64Tgm." (Specification at paragraph [0099]; See lanes #89, #90 and #91 of Figure 3.) Moreover, the male transgenic sgp64 mice showed normal fertility (see Example 3). Thus, the methods of the amended claims allow one of skill in the art to efficiently generate specific antibodies to a desired protein using an immunogen that contains contaminating background antigens, *e.g.*, gp64, and to do so in a line of mice that can be efficiently maintained.

The specification provides substantial guidance regarding the immunogen. The specification describes immunogens in many forms and makes clear that the common feature shared by all these forms is not display on the surface of an intact baculovirus, but rather *the presence of contaminating background antigens*:

> More specifically, examples of the immunogens of the present invention comprise *cells, cell culture solutions, cell lysates, viruses, and crude antigens*, in which membrane proteins may be contaminating as background antigens. ....*Whole cells or viruses as well as portions thereof* can be used as the immunogens. Furthermore, just *cell membrane or viral envelope portions* may be used as the immunogens. When such whole cells or viruses, or portions thereof, such as their cell membrane or viral envelope, are used as the immunogen, membrane proteins comprised in the cell membrane or viral envelope contaminate as background antigens. (Specification at paragraph [0055].) (Emphasis added.)

Upon reading the Applicants' specification, one of skill in the art would recognize that the method of the claims could be used for any immunogen that was contaminated with background gp64 protein. What is claimed is a method for the efficient production of antibodies to a specific immunogen when that immunogen happens to be contaminated with highly immunogenic gp64 protein. Immunization with partially purified proteins or cell lysates is a

method that is routine in the art and one of ordinary skill would readily understand that while the method of the claims could be used for immunogens that included intact baculoviral particles that expressed the target antigen on their surface, it is equally applicable to immunogens comprising a portion of a baculoviral particle, *e.g.*, lysates, extracts or partially purified portions of those same particles, as long as they contained the target antigen. Moreover, while successful immunization with intact baculovirus particles requires the surface display of the target antigen, immunization with portions of a baculoviral particle is not nearly so restricted and can result in the production of specific antibodies regardless of the localization of the corresponding target antigens in the intact particle. In fact, surface localization of the target antigens is largely irrelevant when the immunogen is a baculoviral lysate. In an intact particle, only those proteins on the surface have access to the immune system; once the particle has been fractionated, all proteins, including those found on the inside of the particle become potential targets for recognition by the immune system. Thus, there is no reason to limit the scope of the claims to the "membrane protein" and/or the proteins "displayed on the surface of a baculovirus" as proposed by the Examiner in the interview summary.

The Examiner's concerns regarding the dose of baculoviral particles and the structure of the antigen that was administered to the mice in Example 4 are misplaced. Claim 16 is drawn to a method of producing an antibody that relies on immunizing a particular kind of transgenic mouse ("a transgenic mouse whose genome comprises a nucleic acid sequence encoding baculovirus gp64, wherein the gp64 is soluble and lacks a transmembrane region and wherein the mouse is fertile") with a particlar kind of immunogen ("an immunogen comprising a baculovirus particle or a portion thereof, wherein said particle expresses the target antigen, and wherein said particle or portion thereof comprises gp64 and said target antigen"). The claimed method can be used to generate antibodies against any target antigen as long as it is administered in the context of a baculovirus particle or portion thereof that includes gp64. General methods for preparing baculoviral particles and determining the relevant dosage were routine in the art at the time the application was filed. The specification provides ample guidance for making baculoviral particles and using them to immunize mice in order to practice the method of claim 16 (specification at paragraphs [0059], [0062] and [0066]). One of skill in the art would readily be

able to prepare a budding baculovirus expressing target antigen of interest and use it or a portion thereof in order to immunize the sgp64 mice of the claims without undue experimentation.

Moreover, the Examiner's contention that "applicants do not teach obtaining antibodies against pepT1 or provide adequate guidance that antibodies against pepT1 actually occur" (Office Action at page 3-4) obscures the point that the Example 4 makes. Example 4 was designed to show that when the sgp64 transgenic mice of the claims were immunized with a budding baculovirus that expressed pepT1 (pepT1-BV), such mice were tolerant to gp64, *i.e.*, the sera from the sgp64 transgenic animals contained lower levels of anti-gp64 antibodies than did sera from control non-transgenic animals immunized with the same baculoviral immunogen. Far from weighing against enablement, Figure 4 clearly shows that sgp64 transgenic mice were in fact immunotolerant to the baculoviral antigen, gp64, that contaminates budding baculoviral preparations. The fact that anti-PepT1 antibodies were not assayed in this experiment is largely irrelevant to the enablement of the claims. As discussed above, methods of producing and assaying antibodies had been commonplace for many years at the time the application was filed and based on the teachings in the specification, there is no reason to suspect that others could not similarly make and use the sgp64 transgenic mice to practice the invention of the claims.

Applicant reminds that Examiner that an Applicant enjoys a presumption that the specification, which discloses how to make and use the claimed invention, complies with the first paragraph of 35 U.S.C. § 112, unless there is a reason to doubt the objective truth of the specification. MPEP 2164.04 (citing *In re Marzocchi*, 439 F.2d 220, 224 (C.C.P.A. 1971)). As the MPEP explains, in order to sustain a rejection under enablement rejection, the "factors, reasons, and evidence" leading to the rejection should be provided, "findings of fact" should be "supported by the evidence" and that "specific technical reasons are always required." *Id.*

It is unclear why the Examiner has cited Saitoh as "post-filing evidence of antibodies to pepT1." The Office Action states at page 5:

> Given the lack of teachings in the specification, taken with post filing evidence, the claims should be limited to
>
> While the membrane protein encompasses gp64 baculovirus antigen, which is not a useful target antigen in the method claimed because the specification states the mice are tolerized to gp64, this is considered a non-operative embodiment.

Clarification of this passage is respectfully requested. Contrary to the Examiner's assertion, Siatoh does not disclose "sgp64 transgenic mice" (Office Action at page 4); the Examiner has not explained why Saitoh is relevant to an enablement rejection. In addition, the second sentence of the passage reproduced above is not comprehensible. Applicant notes that the claims do not recite "a membrane protein".

In view of the above, Applicant submits that the specification enables one of ordinary skill in the art, as of the effective filing date, to make and use the invention now claimed without resort to undue experimentation. Applicant contends that the present claims are in condition for allowance, which is respectfully requested.

Double patenting

The Examiner has maintained the provisional obviousness-type double patenting rejections based on claims 22 and 23 of the co-pending Application No. 10/516,603 (the '603 application) (Office Action at page 5). The '603 application recently received a Notice of Allowance. The Examiner has asserted that claims 16-18 of the present application (the '690 application) are not patentably distinct from those of the '603 application because "both require making antibodies against a target antigen using a transgenic mouse expressing gp64 that is immunotolerant to gp64using a "baculovirus or portion thereof" ('690) or a "budding virus or portion thereof" ('603) (Office Action at page 5). Applicant respectfully traverses this rejection.

A non-statutory obviousness-type double patenting rejection is appropriate only where an application claim is not patentably distinct from the reference claim because the application claim is either anticipated by, or would have been obvious over, the reference claim. MPEP 804(II)(B)(1). An obviousness-type double patenting rejection that is not based on anticipation should be analyzed in a manner comparable to the guidelines for an obviousness rejection under 35 U.S.C. § 103(a), considering the following Graham factors: (A) the scope and content of the patent claim relative to the claim in the application at issue; (B) the differences between the scope and content of the patent claim as determined in (A) and the claim in the application at issue; (C) the level of ordinary skill in the pertinent art; and (D) an evaluation of any objective indicia of non-obviousness. Id. Any obviousness-type double patenting rejection must make clear the differences between the inventions defined by the allegedly conflicting claims and the

reasons why a person of ordinary skill in the art would conclude that the invention defined in the claim at issue is anticipated by, or would have been an obvious variation of the invention defined in a claim of the patent. Id.

The present claims specify that the genome of the transgenic mouse comprise a baculovirus gp64 wherein the gp64 is soluble and lacks a transmembrane region. As the Examiner recognizes, the '603 claims recite a gp64 transgenic mouse, but as the specification of the '603 application makes clear, the genome of the gp64 transgenic mice encoded the full-length 512 amino acid coding sequence of baculovirus gp64 (See, for example, Example 1 at paragraph [0130] and Figure 1). The gp64 mice were immunotolerant to baculovirus gp64, but the males of this line tended to be infertile (See, for example, paragraph [0142] and Table 2). The inventors of the present application sought to develop a line of transgenic mice that was immunotolerant to baculovirus gp64, but that retained the fertility of wild-type animals. The inventors found that mice that were transgenic for a fragment of gp64 that corresponded to the extracellular region of gp64, *i.e.*, "soluble gp64," were both immunotolerant to gp64 and fertile. (See for example, specification at paragraphs [0083] and [0093] and Figure 1). One of skill in the art would readily recognize that it is far more efficient to maintain a transgenic mouse line when both males and females are fertile. However, one of skill in the art, after reading the '603 application would not have expected that mice that were transgenic for soluble gp64 would be both tolerant to baculovirus gp64 and fertile. The '603 application does not disclose any domains of gp64, much less the extracellular domain of gp64. There is nothing in the disclosure of the '603 application that would have provided one of skill in the art with any reason to use a soluble gp64 construct in order to retain both the immunotolerance of the gp64 transgenic animals and the fertility of the wild type male animals.

Based on the foregoing, Applicant respectfully submits that the claims of the present application are in no way obvious variants of those in the '603 application. By Applicant's calculations, the filing of a terminal disclaimer would result in the loss of about two years of patent term. Such a loss of patent term is not warranted and the rejection based on obviousness type double patenting should be withdrawn.

CONCLUDING FORMALITIES

Please apply any other charges or credits to deposit account 06-1050, referencing attorney docket number 14875-0167US1.

Respectfully submitted,

/Gretchen L. Temeles/

Date: July 2, 2010

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Attachment: Exhibit A

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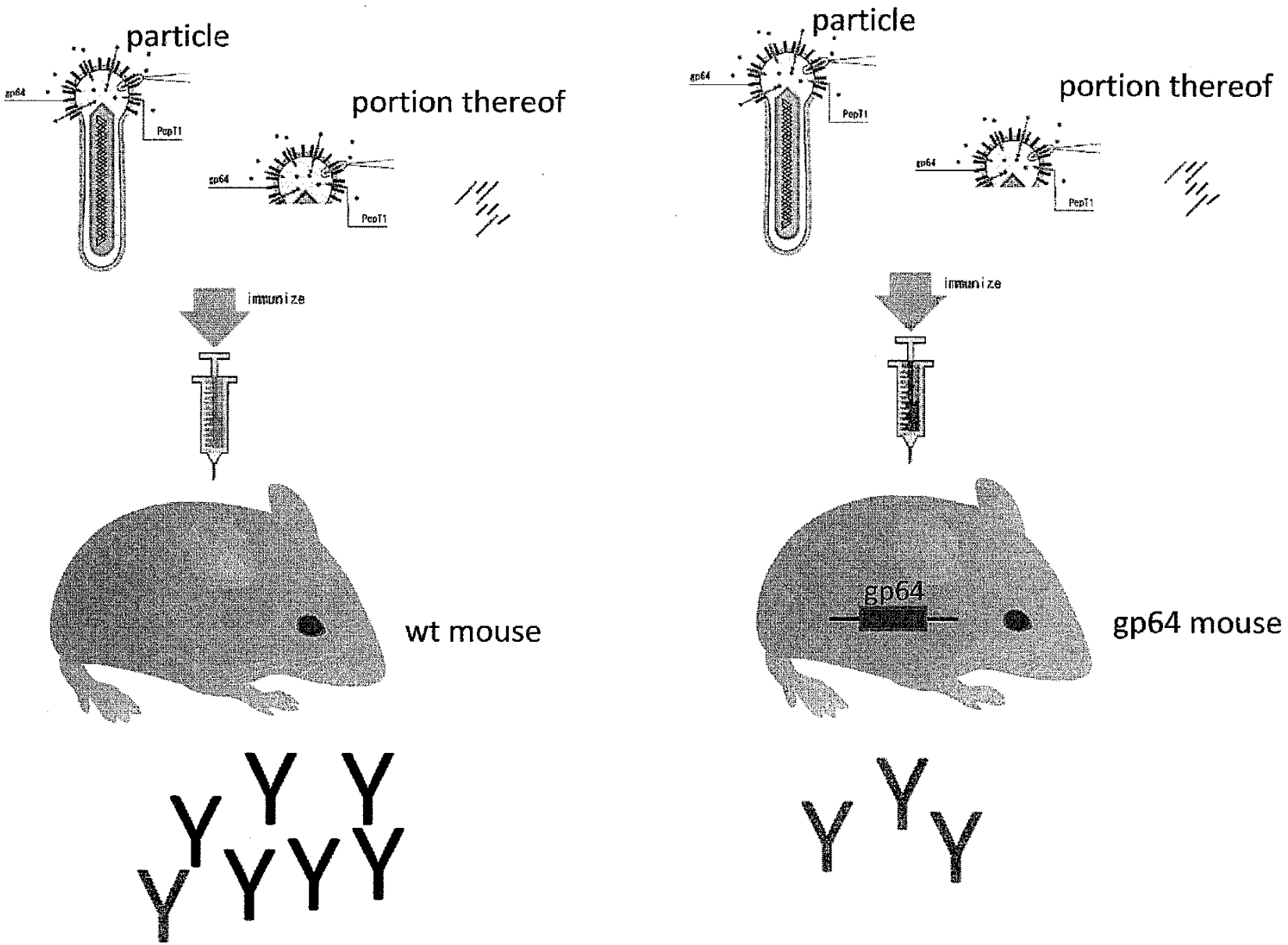
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Exhibit A